

REMARKS**Overview**

Claims 1-8, 10-16, 19-27 and 29-32 are pending in this application. Claims 2, 21, 24, 30, and 32 have been amended. Claims 23, 25-27 and 29 have already been allowed. The present response is an earnest effort to place all claims in proper form for immediate allowance. Reconsideration and passage to issuance is therefore respectfully requested.

Issues Under 35 U.S.C. § 112

Claims 2, 21, and 24 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

In particular, the Examiner indicates that it is unclear whether the logic constraints of claims 2 and 21 are intended to replace the logic constraints of claims 1 and 20, respectively or are intended to be in addition to the constraints of the parent claims. Claims 2 and 21 have been amended to make clear that claims 2 and 21 further define the logic constraints referenced in claims 1 and 20. Therefore, it is respectfully submitted that these issues have been remedied.

With respect to claim 24, it is intended that the language of the claim further define the logic constraints of claim 23. Therefore, claim 24 has been amended to make this clear. Therefore, it is respectfully submitted that this issue has also been remedied.

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With respect to claim 24, it is intended that the language of the claim further define the logic constraints of claim 23. Therefore, claim 24 has been amended to make this clear. Therefore, it is respectfully submitted that this issue has also been remedied.

Additional claim amendments

Claims 30 and 32 have been amended to make minor claim changes. In particular claim 30 has been amended to better relate the last clause to the rest of the claim. Claim 32 has been corrected. These claim amendments are not intended to alter the scope of the claims in any way.

Issues Under 35 U.S.C. § 102

Claims 1-8, 10-12, 14-15, 19-21, and 30-31 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Hatzimanikatis et al. (AIChE Journal (May 1996) Vol. 42, no. 5, pp. 1277-1292). As Hatzimanikatis et al. does not disclose using a flux balance analysis model, let alone modifying such a model, these rejections are respectfully traversed.

Hatzimanikatis et al. describes an optimization strategy that allows the selection of the optimal regulatory structure for a particular metabolic process. This strategy utilizes a mixed-integer linear programming formulation to identify the changes in a given regulatory network necessary to achieve the desired objective. As an example, the optimal regulatory structure for the maximization of phenylalanine production is presented. Inactivation of three of the eight original feedback inhibition loops and over expression of three enzymes would theoretically cause a 42% increase in phenylalanine selectivity.

A flux balance analysis as described in the original specification, p. 2, as a model that "utilizes only the stoichiometric mass balances of the metabolic network and cellular composition information in the absence of detailed kinetic and thermodynamic data, to identify boundaries for the flux distributions available to the cell." Thus, in the FBA modeling approach, the metabolic network is constrained by the balance of the metabolic fluxes (reactions) around each node (metabolite).

Claim 1 requires "constructing a flux balance analysis model; applying logic constraints to the flux balance analysis model." Hatzimanikatis et al. does not disclose these limitations and therefore this rejection to claim 1 must be withdrawn.

The Examiner cites to pp.1282-1283 in support of the rejection and as teaching construction of a flux balance model and applying logic constraints to the flux balance analysis model. Here, Hatzimanikatis et al. merely discloses using the mass balance for each metabolite as a constraint for a metabolic optimization problem. Clearly, the model presented by Hatzimanikatis et al. is a kinetic model and not a flux balance analysis. Although mass balances are used by Hatzimanikatis et al., such use of mass balances does not somehow transform Hatzimanikatis's model into a flux balance analysis. The Examiner is requested to closely review Hatzimanikatis et al. to fully understand the significantly different approach of Hatzimanikatis et al. relative to a flux balance analysis approach and relative to the approach of the present invention. To assist the Examiner and provide further evidence that the Hatzimanikatis et al. approach does not provide for constructing a flux balance analysis, attached at Exhibit 1 is an article which reviews mathematical models that describe the cellular metabolism. Note that the methodology of Hatzimanikatis et al. is characterized as a kinetic modeling method as opposed to a stoichiometric model, let alone a flux balance analysis. Attached at Exhibit 2 is a paper which has two authors in common with Hatzimanikatis et al. and which characterizes Hatzimanikatis et al. as using a kinetic description to define constraints on the optimization in the form of steady-state mass balances of intracellular metabolites.

Thus, it should be clear that Hatzimanikatis et al. discloses neither a flux balance analysis model nor applying logic constraints to the flux balance analysis model. Therefore, this rejection to claim 1 must be withdrawn. As claims 2-5 depend from claim 1, these rejections must also be

withdrawn. As claim 6 also requires "constructing the flux balance analysis model" and "applying a plurality of logic constraints to the flux balance analysis mode", this rejection should also be withdrawn. As claims 7-8 and 10-12, 14-15 depend from claim 6, these rejections must also be withdrawn. As claim 19 requires "a flux balance analysis model" and "a plurality of logic constraints applied to the flux balance analysis model", this rejection to claim 19 should be withdrawn. As claims 20-21 depend from claim 19, these rejections must be withdrawn. As claim 30 requires "constructing the flux balance analysis model" and "applying a plurality of logic constraints to the flux balance analysis model", this rejection to claim 30 should be withdrawn. As claim 31 depends from claim 30, this rejection must also be withdrawn.

Issues Under 35 U.S.C. § 103

Claims 13, 16, and 43 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Hatzimanikatis et al. (AIChE Journal (May 1996) Vol. 42, no. 5, pp. 1277-1292) as applied to claims 1-8, 10-12, 14-15, 19-21, and 30-31. Hatzimanikatis et al. has already been distinguished. In particular, Hatzimanikatis et al. does not use a flux balance analysis model, but instead uses a kinetic model. Thus, Hatzimanikatis et al. uses a completely different approach. Therefore, these rejections must also be withdrawn.

Conclusion

It is respectfully submitted that all pending claims are in proper form for immediate allowance. Reconsideration and passage to issuance are therefore respectfully requested.

Applicant is a small entity; therefore, please charge Deposit Account 26-0084 the amount of \$395.00 to cover the costs associated with the filing of this RCE. This is also a request to

extend the period for filing a response in the above-identified application for one month from November 18, 2005 to December 18, 2005. Therefore, please charge Deposit Account number 26-0084 in the amount of \$60.00 to cover the cost of the one month extension. No other fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Respectfully submitted,



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Enclosures: Exhibit 1
 Exhibit 2